Management of Patients Symptomatically Unresponsive to Levothyroxine: Natural Desiccated Thyroid Extract or the Combination of Levothyroxine and Liothyronine? A Research Priority

Hughes, Dyfrig; Livingston, Mark; Heald, Adrian

Experimental and Clinical Endocrinology & Diabetes

DOI:
10.1055/a-1062-6167

Published: 01/09/2020

Peer reviewed version

Management of patients symptomatically unresponsive to levothyroxine: natural desiccated thyroid extract or liothyronine? A research priority in the light of the 2019 NICE Guidance

Running Head
Treatment resistant hypothyroidism

Dyfrig A. Hughes[1,2] Mark Livingston[3], Adrian Heald[4,5]

Affiliations:

[1] Centre for Health Economics & Medicines Evaluation, Bangor University, Bangor;
[2] Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool
[3] Department of Clinical Biochemistry, Black Country Pathology Services, Walsall Manor Hospital, Walsall;
[4] The School of Medicine and Manchester Academic Health Sciences Centre, University of Manchester, Manchester;
[5] Salford Royal Hospital, Salford;

Corresponding author: Dr Adrian Heald
Department of Diabetes and Endocrinology,
Salford Royal Hospital, Salford, UK.
M6 8HD

Telephone: +44 161 206 5157

Email: adrian.heald@manchester.ac.uk

Keywords:

Primary hypothyroidism, thyroid hormone resistance, liothyronine, natural desiccated thyroid extract

Manuscript word count (main text):

Abstract

Introduction

Around 5-10% of hypothyroid patients continue to experience profound and sometimes disabling symptoms, including fatigue, depression and impaired cognition, in spite of being adequately replaced biochemically.

The use of liothyronine and natural desiccated thyroid extract is controversial for reasons of costs, a lack of evidence of additional benefit over levothyroxine alone, and potential safety concerns.

Methods

We recruited self-selecting patients with the help of a national thyroid charity who reported to be clinically resistant to levothyroxine despite being biochemically euthyroid. They were invited to complete an on-line, validated multi-attribute health utility instrument, the EuroQol EQ-5D-5L questionnaire and accompanying EQ-VAS (visual analogue scale). EQ-5D-5L index values (utilities, a preference-weighted measure of patients' health valuation) were estimated based on the EQ-5D-5L cross walk value set for the UK.

Results

Responses were available from 54 people. Mean (SD, minimum, maximum) EQ-5D-5L utility was 0.53 (0.23, -0.00, 0.84); and EQ-VAS was 49.3 (17.2, 5.0, 90.0). 44/54 (81%) individuals reported having moderate problems in at least one attribute, most often their ability to perform usual activities, and anxiety or depression; 24/54 (44%) reported severe problems; and 6/54 (11%) reported extreme problems.

Conclusion

Reported health utilities in these individuals are comparable to those reported by patients with lung cancer, or acute cerebrovascular disease and rank in the bottom decile of 100 chronic diseases.

A lack of proven effective treatment and a large unmet need indicates that now is the right time for a definitive clinical trial to address this important area of uncertainty.

What is known about this topic?

- A significant minority of patients with hypothyroidism remain symptomatic despite being adherent to, and biochemically controlled with levothyroxine.
- The NHS in the UK prohibits the routine use of liothyronine and natural desiccated thyroid extract for reasons of cost, a lack of evidence of additional benefit over levothyroxine alone, and potential safety concerns.
- There are no clinical trials of liothyronine and natural desiccated thyroid extract in this patient sub-group.

What does this article add?

- Reported health utilities in these individuals are comparable to those reported by patients with lung cancer, or acute cerebrovascular disease and would rank in the bottom decile of 100 chronic diseases.
- Testing whether alternatives to levothyroxine alone are clinically and cost effective is now regarded as a research priority.

1. Introduction

Primary hypothyroidism affects about 3% of the general population (5.1% women and 0.9% men) [1]. The majority of people are treated adequately with levothyroxine (L-thyroxine). However about 5-10% of hypothyroid patients (representing between 75,000 and 150,000 adults in the UK) continue to experience profound and sometimes disabling symptoms, such as fatigue, depression and impaired cognition, in spite of being adequately replaced biochemically [2].

Supplemental liothyronine (L-tri-iodothyronine) plus levothyroxine was originally the treatment of choice when synthetic thyroid hormones first replaced animal thyroid extracts. However, with its more favourable posology and no evidence for any additional benefit of liothyronine, levothyroxine monotherapy became the treatment of choice. Nevertheless, supplemental liothyronine remains a treatment option which has been prescribed by some general practitioners and by endocrinologists across the UK for a long time. A few endocrinologists prescribe natural desiccated thyroid extract (NDTE) with anecdotal evidence of benefit, but which is unlicensed in the UK.

Clinical guidelines that apply in the UK only support the use of levothyroxine, and advise that liothyronine should only to be used in exceptional cases [3-5], principally owing to its high cost. Together, liothyronine and NDTE formulations cost the NHS £35m in 2016. The restriction of liothyronine and NDTE as treatment options led to great consternation among patients, with around 20,000 people signing a British Thyroid Foundation petition for continued access. In response to its consultation on medicines which should not be routinely prescribed in primary care, NHS England received a significant feedback from patients and organisational bodies, which highlighted that “A treatment that leads to improvements in the health-related quality of life of patients with symptoms of hypothyroidism would represent a significant unmet need”. The draft NICE guidance lists, as the first research priority, “What is the clinical and cost effectiveness of levothyroxine and liothyronine combination therapy compared with levothyroxine alone for people with hypothyroidism whose symptoms have not responded sufficiently to levothyroxine alone?”.

2. Review of existing evidence

Thirteen trials using combined liothyronine plus levothyroxine therapy have been reported; 7 cross-over [6-12] and 6 parallel in design [13-18]. Most are underpowered with sample sizes of 10 to 71 [6-10, 14-16]. Although some studies have shown a beneficial effect, such as patient preference for combination therapy or an improved metabolic profile, patients on combination therapy generally do not have improved outcomes compared with those on levothyroxine monotherapy. Among the larger trials, Walsh et al [11] (n=110) found no difference in patient wellbeing, quality of life (Short Form-36, General Health Questionnaire (GHQ)-28, Thyroid Symptom Questionnaire) or cognitive function. Appelhof et al [13] (n=140) reported that for the primary outcome, patients preferred liothyronine plus levothyroxine to levothyroxine alone over 15 weeks but there were no differences in secondary outcomes. In the largest trial [17], which was double-blind and randomised 697 patients, the difference between liothyronine plus levothyroxine and levothyroxine alone in the co-primary outcomes at 3 months was 0.47 points (95%CI, -0.26, +1.12) for the GHQ-12 score; and 0.61 (95%CI, 0.42, 0.90) in the odds ratio for patients scoring ≥3 in GHQ-12. There was a significant difference in Hospital Anxiety and Depression Scale (HADS) anxiety score (odds ratio, 0.55; 95% CI, 0.32, 0.95) but not in other secondary patient-reported outcome measures. Differences in GHQ caseness and HADS anxiety were not apparent after 12 months. A recent pharmacoepidemiological study did not identify any additional risk of atrial fibrillation, cardiovascular disease or fractures with liothyronine [19].

Most studies of NDTE have been uncontrolled and open-label, and compared NDTE with levothyroxine, not in terms of efficacy and safety but in terms of comparative potency, onset and duration of action, and effects on serum lipids [20-23]. There is only one randomised, double-blind, cross-over trial comparing NDTE with levothyroxine [24], but in an unselected population of 70 people with primary hypothyroidism. Following 12 weeks (period 1) and 16 weeks (period 2) of treatment, there were no differences in symptom scores, general health questionnaires or neuropsychological testing between treatment groups. No study patient had a thyroid stimulating hormone level outside of the reference range. No adverse events were reported with any of the treatments; both were tolerated equally well.

3. What we did

We aimed to estimate the health utility of patients with clinically resistant hypothyroidism in order to compare with other chronic diseases, and to estimate the standard deviation of utility values for future trial sample size calculations.

We recruited self-selecting patients who reported to be clinically resistant to levothyroxine despite being biochemically euthyroid, with the help of a national thyroid charity. Patients were invited to complete an on-line, validated multi-attribute health utility instrument, the EuroQol EQ-5D-5L questionnaire and accompanying EQ-VAS (visual analogue scale). The EQ-5D-5L questionnaire asks about 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. EQ-5D-5L profiles were converted to EQ-5D-5L index values (utilities, a preference-weighted measure of patients' health valuation) based on the EQ-5D-5L cross walk value set for the UK.

The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS was used as a quantitative measure of health outcome that reflect the patient's own judgement.

4. What we found

Responses were available from 54 people. Mean (SD, minimum, maximum) EQ-5D-5L utility was 0.53 (0.23, -0.00, 0.84). 44/54 (81%) individuals reported having moderate problems (level scores ≥3) in at least one attribute, most often their ability to perform usual activities, and anxiety or depression; 24/54 (44%) reported severe problems (level scores ≥4); and 6/54 (11%) reported extreme problems (level 5) (Figure 1).

Reported health utilities in these individuals were comparable to those reported by patients with lung cancer, or acute cerebrovascular disease and would rank in the bottom decile of 100 chronic diseases.

The mean (SD, minimum, maximum) EQ-VAS score was 49.3 (17.2, 5.0, 90.0).

5. Why is a further trial important?

Existing trial evidence is insufficient in several respects. Principally and most importantly, the trials did not recruit patients who did not feel significantly better on levothyroxine, and so failed to identify the actual subgroup that could benefit from liothyronine or NDTE. There is also improved understanding of the pharmacology of levothyroxine resistance. L-tri-iodothyronine is the endogenous thyroid hormone,

converted from L-thyroxine by de-iodination. Polymorphisms in the genetic coding of the deiodinase-2 enzyme may reduce L-tri-iodothyronine levels in many tissues, including the brain [25]. This may represent a pharmacogenetic component to non-response to levothyroxine.

Of direct relevance to this letter is that NICE draft guidance [26] has noted the value of a randomised control trial, to assess combination therapy in patients how remain symptomatic in spite of apparently adequate levothyroxine replacement. We suggest that it is now the right time to determine whether the alternatives to levothyroxine alone result in any benefit to patients who do not achieve adequate symptom resolution with this treatment. Results would also inform policy worldwide.

6. Conclusion

As the first assessment of EQ-5D-5L utilities in a patient group with resistant hypothyroidism, our findings provide a basis for powering a trial of alternative treatment options to levothyroxine. Reported health utilities in these individuals are comparable to those reported by patients with lung cancer, or acute cerebrovascular disease and would rank in the bottom decile of 100 chronic diseases.

The management of patients who are biochemically well-controlled with levothyroxine but who remain symptomatic is challenging and often unsatisfactory for patient and clinician alike. The controversy and uncertainty surrounding the benefits and cost-effectiveness of supplemental liothyronine and NDTE are well recognised. Liothyronine is clinically effective but is not considered to be cost-effective because of relentless price inflation, although there is a lack of economic evidence.

A robust evaluation of the clinical and cost-effectiveness of treatment options is necessary to determine whether any additional benefits of alternatives to levothyroxine justify the additional cost in patients who are seemingly resistant to conventional therapy with levothyroxine alone. This proposal has recently been supported by the NICE draft guidance for thyroid management [26].

Conflict of interest: No author has any conflict of interest

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Figure 1. Distribution of responses to each dimension of the EQ-5D-5L